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Results of Catheter-directed Endovascular Thrombolytic Treatment of Acute Ischaemia of the Leg

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Abstract *Objectives:* To observe immediate and late results of catheter-directed endovascular thrombolytic treatment of acute ischaemia of the leg.
Design, material and methods: A total of 212 patients treated with Actilyse® at the University Hospital of North Norway because of acute arterial ischaemia of the leg during the period 01 January 2000–30 June 2006 were analysed retrospectively.
Results: The radiologic outcome was judged to be successful in 101 (48%), adequate in 80 (38%) and failed in 31 (14%). At 1-year follow-up, 158 (75%) were alive without amputation, 14 (7%) were alive with amputation, 20 (9%) were dead without amputation and 20 (9%) were dead with amputation. Altogether, 34 (16%) were amputated and 40 (19%) were dead after 1 year. After an average observation period of 3.25 years, 111 (52%) were alive without amputation, 16 (8%) were alive with amputation, 60 (28%) were dead without amputation and 25 (12%) were dead with amputation. A total of 41 (19%) were amputated and 85 (40%) were dead. Fifty complications were registered; 30 (14%) patients had a compartment syndrome, eight (4%) had cerebral stroke and 12 (6%) had a myocardial infarction.
Conclusions: The results are at least as good as historic controls and similar to international series. Especially, it appears as though the long-term results are somewhat better. The complication rate and morbidity are less than in surgery alone.

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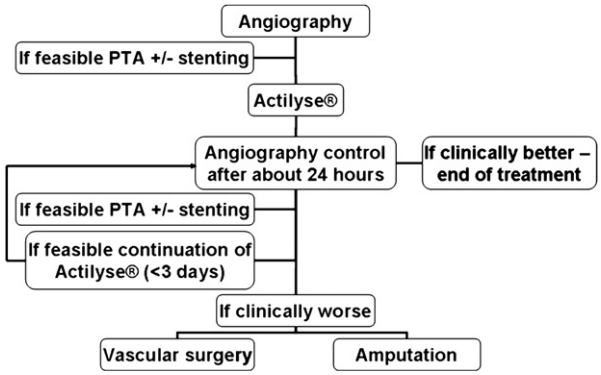

Figure 1 Treatment algorithm for acutely ischemic legs. The terms "clinically better" and "clinically worse" were based on the patients' subjective experience of increased/decreased pain and function together with changes in common clinical signs.

Until the 1990s, the treatment of acute arterial ischaemia of the lower leg consisted primarily of surgery, that is, embolectomy, reconstruction and/or amputation. Gradually fibrinolysis took over and after the introduction of human plasminogen activator (rt-PA), the algorithm of treatment at most places has been catheter-directed infusion of rt-PA, immediately following primary angiography. Actilyse® is a human plasminogen activator which clears the cross-linked fibrin mesh of the clot. A catheter is introduced via the contralateral iliac artery and directed close to or preferably into the thrombus. Infusion into the clot facilitates the lytic process.[1] During the same procedure, the patient can also have percutaneous transluminal angioplasty (PTA), and many are also stented and/or undergo vascular surgery (Fig. 1). We have looked at immediate and late results of this treatment from a representative period where all legs with acute ischaemia underwent this approach.

Acute ischaemia of the leg is defined as any reduction or impairment of perfusion to the lower extremity, severe enough to represent a potential threat to the survival of the leg.[2]

The common cause of this condition is arterial occlusion due to thrombosis and/or embolism.

Material and Methods

A total of 212 patients treated with catheter-directed thrombolysis (Actilyse® Boehringer Ingelheim, Ingelheim am Rein, Germany) at the University Hospital of North Norway (UNN) because of acute arterial ischaemia of the leg during the period 1 January 2000—30 June 2006, were analysed retrospectively. Only patients who received primary thrombolysis were included. Those who underwent initial vascular surgery alone were excluded and were not counted. Furthermore, transitional patients passing through the catchment area of the hospital at the incident (four patients) were excluded, due to problems with follow-up.

Figure 2 57 year old male with multiple embolic incidents. Acute symptoms in the left leg, successfully treated with catheter-directed thrombolysis. Further examination revealed cardiac origin of embolies.

Table 1 Immediate results of treatment in relation to clinical and demographical factors in 212 patients. Successful, adequate and failed refer to initial angiographic results and are given in percent.

	Successful N = 101 48	Adequate N = 80 38	Failed N = 31 14	*p*-value
Age				
<75 yrs	65	56	58	0.43
≥75 yrs	35	44	42	
Sex				
Male	62	64	74	0.47
Female	38	36	26	
Symptoms & signs				
Rest pain	55	69	71	0.08
Cold leg	80	85	84	0.68
Paresthesia	34	33	32	0.98
Ischemic ulcer	17	29	23	0.16
Distal run-off				
No open art.	9	26	35	<0.01
One open art.	19	35	26	
Two open art.	52	28	23	
Three open art.	20	11	16	
Occlusion length				
<10 cm	34	30	19	0.32
≥10 cm	66	70	81	
Causes				
Thrombosis	37	50	58	0.14
Embolism	42	29	29	
Emb. on thromb.	21	21	13	
Supplementary treatments				
PTA	82	69	48	<0.01
Stent	36	24	16	0.06
Vascular surgery	34	45	74	<0.01
Fasciotomy	11	18	26	0.11
Amputation	6	25	48	0.01

Each patient underwent a diagnostic arteriogram to demonstrate the level of occlusion, usually from the contralateral groin approach. A guide wire was usually passed through the length of the occlusion before the initiation of the infusion. A catheter system with multiple side holes was used (UNI*FUSE™, AngioDynamics Inc, Queensbury, NY, USA or Cragg-McNamara™, Micro Therapeutics Inc., Irvine, CA, USA). After the insertion of the thrombolytic catheter, a bolus of 5 mg alteplase (Actilyse®) and 5000 IU unfractioned heparin were injected through the catheter at the start of the procedure, followed by continuous infusion of alteplase 0.01 mg kg^{-1} h^{-1} and UFH 300 IU kg^{-1} 24 h^{-1}. After 12—24 h, another arteriogram was made to evaluate therapy. Before catheter withdrawal, PTA was carried out if a significant stenosis was observed (Fig. 2).

The information needed for the study was collected from the patients' files. The immediate results were characterised by the interventionist as successful (contrast in all three leg arteries), adequate (some increase of contrast in the leg arteries) or failed (no contrast). The late results were defined as being alive or dead or whether the patient had undergone amputation or not. These results were observed 1 year after the first treatment, and then after a mean observation period of 3.25 years.

For all the patients in our group, indications for thrombolysis were present, as revealed by angiography. As for the severity of the ischaemia, we registered clinical symptoms and signs as rest pain, cold leg, paresthesia and ischemic ulcer, distal run-off and occlusion length. The study was approved by the regional ethical committee and was granted dispensation from professional secrecy by the Norwegian Directory of Health. The chi-square test was used for the statistical calculations, and the level of significance was set at $p < 0.05$.

Results

Among the 212 patients, there were 137 (65%) males and 75 (35%) females. Mean age was 72 years with a spread from 30 to 95 years. Among the males, the mean age was 70 years with a spread from 30 to 90 years, and among the females the mean age was 74 years with a spread from 40 to 95 years. Significantly, more men received their first treatment before the age of 75 years. This was not the case with the women. We have no information about the number of patients excluded from thrombolysis because of contraindications.

The radiologic outcome was judged to be successful in 101 (48%), adequate in 80 (38%) and failed in 31 (14%) (Table 1). At 1-year follow-up, 158 (75%) were alive without amputation, 14 (7%) were alive with amputation, 20 (9%) were dead without amputation and 20 (9%) were dead with amputation. All together, 34 (16%) were amputated and 40 (19%) were dead after 1 year. After an average observation period of 3.25 years, 111 (52%) were alive without amputation, 16 (8%) were alive with amputation, 60 (28%) were dead without amputation and 25 (12%) were dead with amputation Table 2. A total of 41 (19%) were amputated and 85 (40%) were dead (Table 3) Fifty complications were registered; 30 (14%) patients had a compartment syndrome, eight (4%) had cerebral stroke and 12 (6%) had a myocardial infarction. No larger bleedings from target or access vessels were recorded. There were significantly more amputees among the dead as compared with those still alive.

Of the 212 patients, 95 (45%) cases were due to local thrombosis in diseased arteries, 75 (35%) were of embolies origin in non-diseased arteries and 42 (20%) were embolies on thrombosis.

A successful radiologic result was the most important predictor of a good late result (Table 3). Other favourable factors influencing the late result were a good distal run-off and an occlusion length less than 10 cm. A poor radiologic result predicted a bad long-term outcome. Other negative factors for the late result were co-morbidities such as angina pectoris and previous myocardial infarction and/or

Table 2 Late clinical results (in %) of 212 patients at 3.25 years in relation to clinical and demographic factors. *Numbers too small for exact calculations.

	Alive −amp N = 111 52	Alive + amp N = 16 8	Dead −amp N = 60 28	Dead + amp N = 25 12	*p*-value
Age					
<75 yrs	74	69	45	36	<0.01
≥75 yrs	26	31	55	64	
Sex					
Male	66	87	62	52	0.13
Female	34	13	38	48	
Symptoms & signs					
Rest pain	56	75	63	80	0.09
Cold leg	75	100	92	84	<0.01
Paresthesias	33	44	28	36	0.67
Ischemic ulcer	17	31	15	56	<0.01
Comorbidity					
Hypertension	68	75	67	60	0.79
Diabetes	14	25	12	24	0.36
Angina pectoris	28	25	45	32	0.12
Previous MI	28	31	45	20	0.07
Atrial fibrillation	23	13	33	36	0.16
Distal run-off					
No open art.	10	49	23	32	<0.01*
One open art.	23	25	30	32	
Two open art.	44	13	40	28	
Three open art.	23	13	7	8	
Occlusion length					
<10 cm	38	19	25	16	0.06
≥10 cm	62	81	75	84	
Causes					
Thrombosis	41	63	38	68	<0.01
Embolism	33	12	52	20	
Emb. on thromb.	26	25	10	12	
Supplementary treatments					
PTA	79	56	63	72	0.39
Stent	33	6	25	28	0.13
Vascular surgery	37	88	38	60	<0.01
Fasciotomy	11	63	8	24	<0.01*
Immediate results					
Successful	60	13	48	16	<0.01
Adequate	35	32	35	60	
Failed	5	65	17	24	

Table 3 The clinical results in % after primary treatment as angiographically revealed at 1 year follow-up and after an average observation period of 3.25 years.

Immediate results	Clinical result	1 yr follow-up	3.25 yrs follow-up
Successful	Alive −amp	81	65
N = 101	Alive + amp	3	2
48%	Dead −amp	14	29
	Dead + amp	2	4
Adequate	Alive −amp	71	49
N = 80	Alive + amp	10	6
38%	Dead −amp	11	26
	Dead + amp	8	19
Failed	Alive −amp	49	19
N = 31	Alive + amp	29	29
14%	Dead −amp	10	32
	Dead + amp	13	19

symptoms and signs of peripheral arterial insufficiency (cold leg and/or ischemic ulcer). Patients who received vascular surgery also had a worse late result. Because complex vascular disease itself is a negative prognostic factor, the patients with more advanced disease will undergo vascular surgery to a higher degree.

An intra-thrombotic position of the catheter tip was necessary for a successful thrombolysis. Good distal run-off prior to intervention resulted in significantly more successful thrombolysis (Fig. 3). The patients in which primary thrombolysis failed would later undergo significantly more vascular surgery and amputations (Fig. 4). A similar tendency was found for fasciotomy.

Discussion

The primary success rate of thrombolysis varies from 65% to 90% in comparable studies.[3–5] In our study, the success rate was 85%. In these studies, the radiologic results were classified as 'successful' or 'failed'. To compare our study with these, we decided to merge the categories 'successful' and 'adequate'. Furthermore, we have to assume that the terms 'successful' and 'adequate' are assessed slightly differently among different interventionists. The results are at least as good as historic controls and similar to international series.[3,4] Especially, it seems as though the long-term results are somewhat better. In an international consensus published in 2007[5] with comparable patient cohorts, the 1-year outcome of acute ischaemia was as follows: alive without amputation 45% (in our study 74%), amputated 30% (in our study 7%) and dead 25% (in our study 19%). These differences exist in spite of the fact that we have included even minor amputations of toes, while the comparable studies have only registered thigh and lower leg amputations. We have no good explanation for these differences, apart from an improved therapeutic approach. We have no reason to assume that our cohort was significantly different from the others in any respect (age, diabetes, smoking, heart failure, etc.). As in other similar series, a generalised atherosclerosis predicts a relatively poor outcome. All the patients received the same dosage of 5000 IU unfractioned heparin through the catheter at the start of the thrombolysis. We have not analysed whether a lower dose would yield fewer failures, because of heparin competing with fibrin in binding rt-PA.

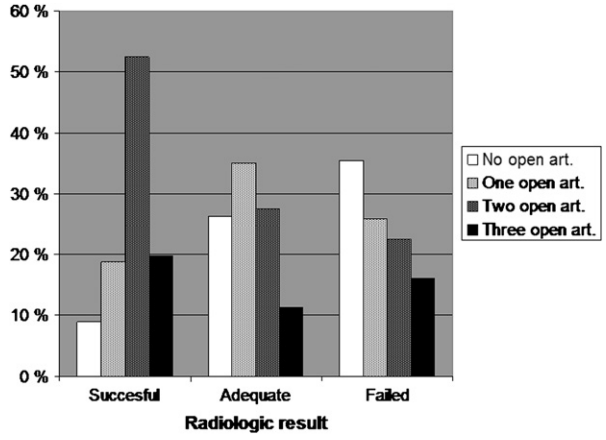

Figure 3 Relationship between distal run-off and immediate results of treatment.

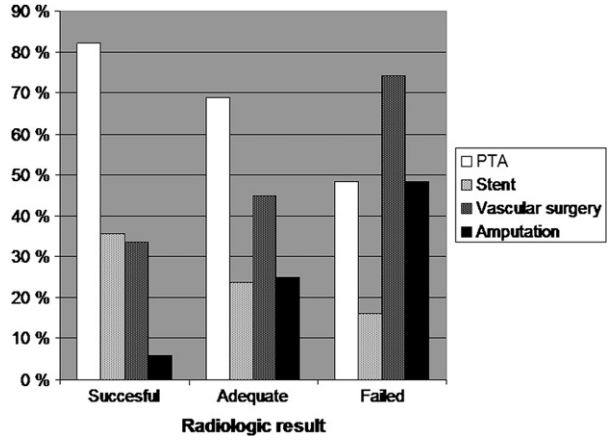

Figure 4 Supplementary treatments (PTA, stent, vascular surgery and/or amputation) in relation to the immediate results of treatment.

There is a majority of males in the study and they were treated at an earlier age than the females. This is also known from previous studies.[4,6,7] In general, males have an earlier onset of lifestyle diseases than females. The link between good distal run-off and successful thrombolysis has also been shown in a previous study.[1]

This retrospective study of a consecutive series of acutely ischemic legs shows that catheter-directed endovascular thrombolytic treatment results in better short- and intermediate-term results. Both complication rate and morbidity were lower than after surgery alone, as reported from similar series. The algorithm requires available intervention competence at any time throughout the year, together with close monitoring of the patient during and immediately after thrombolysis. The approach is in line with contemporary international consensus.[5]

Conflict of Interest/Funding

None.

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